REMARKS

Claim 11 has been amended so that the specificity and sensitivity refer to the expression measurements recited in the parent claim. Support for this amendment is found at page 50, line 25. Accordingly, no new matter is presented.

Claim 21 has been amended so that the tissue sample taken is a human sample and PLAB and L1CAM gene expression are measured. Support for these amendments is found at page 50, line 11-16. No new matter is presented.

Indefiniteness Rejection

The Examiner rejected claims 11-18 and 89-90 as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed for the following reasons.

The rejected claims have been amended so that they refer to the sensitivity and specificity of the measurements of the over-expressed genes of the assays/methods. All measurements have a sensitivity and specificity. They are *attributes* of quantitation. These attributes are present in the independent claims (whether stated or not) and referencing them with respect to expression measurement is appropriate. Accordingly, this rejection is overcome by the amendments.

Non-Enablement

The Examiner rejected claims 1, 3, 6-34, 73, 75, 78-92 and 101-106 as non-enabled. This rejection is respectfully traversed for the following reasons.

The enablement requirement of 35 USC § 112 is satisfied if one of skill in the art can determined how to make and use the claimed invention from the description without the need for undue experimentation. This requirement is met as long as there is direction and guidance for

doing so that is calibrated to the appropriate level of skill in the art in light of the degree of predictability of the art in question. The relationship between what is claimed and what is demonstrated (e.g. in working examples) need only be one in which they reasonably correlate. There is no requirement to present human clinical studies such as one might provide the FDA.

The claims of the instant invention are directed to a PCR reaction for detecting the expression of two genes, PLAB and L1CAM, and indicating the presence of melanoma if their expression is above a cut-off. PCR for detecting gene expression is well known. Nevertheless, a preferred PCR assay is described in detail in Example 7 at page 48 . Both genes are described with specificity. Page 19. Establishing cut-offs for diagnostics is standard practice. Still, this is described in detail at page 46, line 7 and page 48, line 25- page 53, line 5. The correlation between over-expression of the two genes and the presence of melanoma is described at page 27, line 27; page 44, line 20; page 48, lines 15-21. Additionally, correlation of over-expression of PLAB and L1CAM genes and the presence of melanoma is established by (among other things) simultaneous testing using the current standard diagnostic techniques (H&E and IHC). Page 10, lines 8-20; page 27, lines 10-19. Lastly, the PCR assay was validated according to accepted statistical methods and results are shown in Example 6. How one makes and uses the invention is thus plainly described in the specification.

In discussing the breadth of the claims and the working examples, the Examiner states that both non-human and human sampling must be described. For the purposes of the claims currently under consideration, non-human sampling need not be considered especially in view of the amendments provided above. The Examiner further asserts that "a robust" correlation is required between gene expression and melanoma. It is unclear just what constitutes such a correlation but, whatever robust might be, it is not required. The correlation that is required is a reasonable one and this is provided by demonstrating differentiation of melanoma from benign conditions using standard tests of statistical significance and correlation with diagnostic tests that are currently being used in clinical practice as described in the paragraph above. Moreover, the claims are to a method "of identifying melanoma" so it is not clear where the Examiner's assertion about determining "the stage and severity…[and distinguishing] benign melanocyte, or normal tissue" comes from. The Working Examples are criticized by the Examiner on similar

grounds. In either case, the *claimed invention* must be enabled not some other aspect of the invention that is not claimed. "Identifying a melanoma" is enabled whether or not determining stage and severity and the like are enabled and that is all that is required.

In describing the state of the art, the level of skill in the art, and the level of predictability associated with them, the Examiner maintains that the claims include "any amount of increase or decrease" in gene expression. This is a mistaken construction since it is only if expression exceeds a pre-determined cutoff that one determines the presence of melanoma. Establishing cut-off levels is a routine practice in diagnostic medicine. While the claims are not limited to embodiments in which a ten fold increase in expression is seen, it is certainly the case that the examples show how to create a cut-off based on such criteria. Moreover, the general method for establishing a cut-off is described in detail as described above. This is also seen, for example, at page 49, lines 25 *et. seq*.

The Examiner further notes that McMaster describes the unpredictability of PCR as a tool for *staging*. That may be true or it may be more related to inherent difficulties in prescribing molecular meaning to various clinically established stages. In any event, it is not relevant to the issue here since the claimed invention is directed to determining the *presence* of melanoma and that is what must be (and is) enabled.

The Examiner also cites art (Pusztai and Hess as well as Golub) for the proposition that "independent sets of cases" are required to validate PCR markers. Additionally, art (Hilari) is cited as showing that the PLAB and L1CAM are not good markers for melanoma. Taking the last issue first, it is respectfully submitted that this is a confusion between enablement and obviousness. Hilary should be read to say that there is art that teaches away from the very thing the inventors have discovered. This is a case for nonobviousness and has no bearing on enablement; Hilary cannot be used to show that the inventors did not teach how to make and use the claimed invention. That others have proposed gene markers that turned out not to be as discerning as desired is also of no moment. As noted in the specification, the methods used to establish a correlation between the markers and the presence of melanoma are well accepted. Indeed, they were compared with similar testing done on other accepted melanoma markers.

See, e.g., the comparison with *Rimboldi* at page 50, line 19. Further, as noted above, correlation between the methods of the invention and "gold standard" diagnostics was reasonably established. Page 27, line 14, *et. seq*.

Having demonstrated that all relevant inquiries into enablement have been satisfied and that each of the Examiner's points of contention are overcome, this rejection is overcome and a timely notice of allowance is therefore solicited.

The Commissioner is hereby authorized to charge our deposit account 10-0750/VDX5006USPCT/TFV for the costs incurred with this filing. If there are any additional charges or credits in connection with this filing, the Commissioner is hereby authorized to charge/credit the deposit account listed above.

Respectfully submitted,

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